Title: Comparison of all-cause and cause-specific mortality of persons with traumatic spinal cord injuries to the general Swiss population: Results from a national cohort study

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Short title: Cause-specific mortality after TSCI

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1. ABSTRACT

***Background*:** Traumatic spinal cord injuries (TSCI) are a neurological condition associated with reduced well-being, increased morbidity and reductions in life expectancy. Estimates of all-cause and cause-specific mortality can aid in identifying targets for prevention and management of contributors for premature mortality.

***Objectives*:** To compare all-cause and cause-specific rates of mortality to that of the Swiss general population; to identify differentials in risk of cause-specific mortality according to lesion characteristics.

***Methods*:** All-cause and cause-specific standardized mortality ratios (SMRs) were calculated using data from the Swiss Spinal Cord Injury (SwiSCI) cohort study. Cause-specific subhazard ratios (sHRs) were estimated within a competing risk framework using flexible parametric survival models.

***Results*:** Between 1990 and 2011, 2'492 persons sustained a TSCI, of which 379 died. Persons with TSCI had a mortality rate more than two times higher than that of the Swiss general population (SMR=2.32; 95% CI=2.10-2.56). Tetraplegic lesions were associated with an increased risk of mortality due to respiratory and cardiovascular diseases, infections, and accidents. Cause-specific SMRs were notably elevated for SCI-related conditions such as urinary tract infections and septicemia.

***Conclusions*:** Elevated SMRs due to cardiovascular disease, urinary tract infections and septicemia-related mortality suggest the need for innovation when managing associated secondary health conditions.

2. Introduction

In a recent re-evaluation of the WHO Global Burden of Disease study [1], neurological diseases were identified as the leading contributor to the global burden [2]. With overall global aging, the number of people affected with neurological diseases is only expected to augment, regardless of notable reductions in age-standardized rates [2]. Traumatic spinal cord injuries (TSCIs), comprised within the assemblage of neurological diseases, are a disabling condition associated with reduced functioning, and quality of life, increased morbidity, and reductions in life expectancy. In comparison to the general population, persons with TSCI have a roughly 2.5 times greater risk of mortality (standardized mortality ratio [SMR]=2.5, 95% confidence interval [CI]=1.9-3.2) [3]. This burden of mortality is similar to what has been estimated for other chronic neurological conditions such as multiple sclerosis (MS) (SMR=2.8, 95% CI=2.7-2.9) [4] or traumatic brain injury (TBI) (SMR=2.3; 95% CI=2.1-2.4) [5].

Reductions in premature mortality associated with neurological diseases would aid in reduction of global burden of disease. Unfortunately, most research on long-term mortality risk post-SCI have found little to no improvements in recent decades [3], and although persons with SCI have the potential for a life expectancy similar to that of the general population, within-population and between-country discrepancies in mortality and survival estimates exist [3,6]. Importantly, these discrepancies reflect the influence of SCI characteristics and health systems on risk of mortality, and can thereby be exploited to identify targeted interventions and areas for innovation. To this aim, estimates of all-cause and cause-specific mortality can aid in identifying targets for prevention and management of contributors for premature mortality. Furthermore, cause-specific mortality comparisons to the general population can help with benchmarking to identify target areas for health system improvement. The purpose of this study is to thereby provide cause-specific mortality estimates within the SCI population as well as in comparison to the general population.

3. Methods

Study population

The present study employs data collected in the Swiss Spinal Cord Injury (SwiSCI) cohort on incident cases of TSCI admitted to a specialized rehabilitation facility between 1990 and

2011 [7]. Information on cause of deaths (CoDs) was obtained through probabilistic linkage [8] with the Swiss National Cohort (SNC) based on date of birth, date of death (when available), geocoded address, age and sex; applying a similar methodology as that used in previous studies [9,10]. New cases of SCI admitted to an active specialized rehabilitation facility within Switzerland were eligible for linkage. Of the original 6'162 cases, including incident cases of non-traumatic and traumatic SCI from pre-1960, 85.5% were linked (N=5'266) to the SNC data. A weight was created corresponding to the likelihood of a correct match for persons within the SwiSCI dataset with multiple potential matches (21.6%). Records with the highest weight were used in analyses, secondary matches – alternative links – were included in a sensitivity analysis.

Causes of death

For each linked mortality record, up to five causes or contributing causes of death were recorded using ICD-8 (until 1994) and ICD-10 coding (1995 and later): the underlying CoD; the initial cause of disease; the consecutive disease; and two concomitant diseases. Previous studies using CoD information have used the underlying cause of death for analyses, which is defined as the disease or injury that initiated events leading to death, including chronic conditions [11]. A hierarchical approach was used to identify the CoD relevant for cause-specific mortality analyses and the calculation of SMRs, as implemented in previous studies [12]. This approach skips over CoDs related to an external injury code (e.g., sequelae from traffic accident) or SCI-related ICD code to identify a CoD relevant for secondary prevention. For example, when using this hierarchical approach, a CoD coded as „paraplegia/tetraplegia" or „external injury" at the primary, secondary, or tertiary level was ignored until a code unrelated to SCI was identified, if available.

A categorical variable was created to group causes of death into six broad categories based on expert opinion, previous literature [13], data availability, as well as identifying meaningful groups for targeted prevention. These groups include: respiratory diseases (ICD-10 codes=J30-J99 – excluding respiratory infections); cardiovascular disease (I00-I99); neoplasms (C00-D49); infections (including respiratory and urinary tract infections (UTI): A00-B99, J00-J22, N390-392); accidents (S00-Y99, excluding X60-X84); and all other causes of mortality.

Statistical analysis

Standardized mortality ratios (SMRs) were calculated using mortality rates for the general population (GP) (obtained through the SNC) stratified by age, sex, year, and CoD. Flexible parametric models within a competing-risk framework were used to estimate cause-specific subhazard ratios (sHRs) [14]. Separate baseline hazards were estimated for circulatory and respiratory diseases, as well as accidents and all other causes to allow for potential time-varying effects according to cause of death. Attained age, lesion level and completeness were assumed to have an influence on cause-specific mortality, and were therefore interacted with each CoD to allow for the effect of these covariates to vary according to CoD. Attained age at death or study end was accomplished with data splitting techniques.

Given the potential for coding inaccuracies in CoD statistics, two plausible alternative coding scenarios were implemented to evaluate the robustness of results:

- *Sensitivity analysis 1*: Re-calculation of SMRs using the original underlying CoD, not applying hierarchical coding scheme (Supplementary Table 1)
- *Sensitivity analysis 2*: Competing-risk analysis for pre-identified SCI-related causes of interest (i.e., respiratory infections and UTI/renal failure) recorded *anywhere* on death certificate (i.e., underlying CoD, initial disease, consecutive, or concomitant) (Supplementary Table 2 and 3).

All analyses were carried out using Stata version 14.2 [15].

4. Results

Summary statistics

Between 1990 and 2011, 2'492 persons were admitted for first rehabilitation within a specialized rehabilitation center; of which, 379 had a known date of death, contributing to 20'099.9 years of follow-up time. Cause of death information was available for 335 cases. Excluding deaths due to accident- or SCI-related ICD-10 codes, cardiac disease (11.9%), ischemic heart disease (10.1%), neoplasms (8.1%), and suicide (6.3%) were the most commonly recorded CoDs (Table 1). Accidents were less frequently recorded when excluding deaths that occurred less than one year post-injury (Table 1).

The overall mortality rate for persons with TSCI was more than two times higher than that of the Swiss GP (SMR=2.32; 95% CI=2.10-2.56) (Table 2). SMRs were elevated for women (SMR=2.61; 95% CI=2.18-3.13) and tetraplegics (SMR=2.65; 95% CI=2.31-3.04) (Table 2). The synergistic influence of lesion level and completeness on mortality rates was evidenced in that the mortality rate for incomplete paraplegics was 1.6 times that of the GP (SMR=1.64; 95% CI=1.32-2.03), while for complete tetraplegics, the difference was 8.5 times higher than that of the GP (SMR=8.49; 95% CI=6.55-11.01) (Table 2).

Cause-specific mortality

Cause-specific SMRs are presented in Table 3. Relative to the GP, persons with TSCI experienced the highest burden of mortality due to septicemia-related deaths (SMR=19.71; 95% CI=9.40-41.35) (Table 3). With the exception of a few specific causes of death (e.g., chronic obstructive pulmonary disease and neoplasms), mortality rates for persons with SCI were higher overall in comparison with the GP (Table 3). For example, persons with SCI experienced mortality rates due to cardiovascular disease 2.7 times greater than that of the general population (SMR=2.67, 95% CI=2.23-3.19; including cardiac disease, ischemic heart disease, and all circulatory diseases). Cause-specific SMRs further varied according to SCI characteristics (Table 4). When not applying a hierarchical coding scheme, SMRs for accidents and nervous system-related diseases augmented, while SMRs estimated for respiratory infections, other respiratory and other circulatory diseases diminished and were no longer different than mortality rates experienced by the GP (Supplementary Table 1).

Subhazard ratios are presented in Table 5. Regardless of specific CoD, sHRs were highest for the oldest age group (60 years and older) (Table 5). Following adjustment, tetraplegic lesions were associated with an increased risk of mortality due to respiratory and cardiovascular diseases, infections, and accidents (Table 5). Complete lesions were also associated with an elevated risk for mortality due to respiratory diseases and accidents (Table 5). With the exception of age, there was no difference in risk of mortality due to neoplasms or other causes according to lesion characteristics. In a separate analysis on risk of mortality due to respiratory infections, sHRs were elevated for both for tetraplegic and complete lesions (Supplementary Table 2). This relationship remained when including all individuals with a respiratory infection coded on the death certificate, regardless of the

position (Supplementary Table 2). No differential in risk of mortality due to UTI/renal failure was identified according to lesion characteristics (Supplementary Table 3).

5. Discussion

Persons with a TSCI have a more than doubled rate of mortality in comparison with the GP, with augmenting disparities associated with increasing severity. Furthermore, cause-specific SMRs as well as risk for cause-specific mortality varied according to lesion level and completeness, with tetraplegic and complete lesions exhibiting a higher risk in mortality due to respiratory and cardiovascular disease, infections, and accidents in comparison with paraplegic and incomplete lesions.

Cardiovascular diseases, suicide, and systemic infections are the leading causes of death in the present study population when excluding accident and nervous system-related ICD codes. In comparison with previous studies, some discrepancies in leading causes of death can be noted; for example, Savic *et al* reported respiratory diseases (including infections), circulatory diseases and neoplasms as the leading causes of mortality for individuals who survived at least one year post-injury [13]. Additionally, in terms of direction and magnitude of the effect, differences exist between country-level comparisons of cause-specific SMRs. For example, in the United States, DeVivo *et al* reported a higher rate of cancer-related mortality among the SCI population compared to the GP, and reported SMRs nearly half that of what was estimated in this study for suicide [16]. In contrast, two studies from Estonia and Norway estimated similarly heighted suicide-specific SMRs compared with the present study [17,18]. Such differences could be impacted by incomplete and poorly informed coding practices of death certificates [19]. Age- and sex-specific mortality stratified by ICD-10 coding groups for the European standardized population could help improve comparability between countries, and thereby aid in benchmarking across health systems for chronic disease populations.

Mortality rates between two- to three-times that of the GP have been regularly reported in recent SCI literature [3]. Unfortunately, despite advances in medical technology and rehabilitation, a multitude of studies have found only limited or no improvement in long-term mortality [20,21]. The cause-specific SMR estimates reported in this study help identify potential causes that may be driving the overall mortality differential. For example, not only was cardiovascular disease the leading CoD, but also persons with SCI were found to have

about a 2.5 times greater risk of mortality due to cardiovascular disease in comparison with the GP. Modifications in cardiovascular disease risk post-SCI is likely related to physiologic changes associated with lesion level and severity. For example, immediately following SCI, the autonomic nervous system (ANS) incurs physiological alterations that have both acute and chronic implications on cardiovascular functioning, such as unstable blood pressure, autonomic dysreflexia (AD) and orthostatic hypotension (OH), associated with a multitude of cardiovascular complications, including cardiac arrest, intracranial hemorrhage, stroke and death [22]. Reflecting the influence of lesion characteristics on the risk of cardiovascular disease, autonomic dysreflexia – a response to stimuli below the lesion level characterized by an acute elevation of the systolic blood pressure – has been estimated to be three-times more common in individuals with complete tetraplegic lesions in comparison to individuals with incomplete lesions, with AD occurring primarily in high thoracic (paraplegic) and cervical (tetraplegic) lesions [22]. However, although pharmaceutical interventions and guidelines are available for management of AD, persons with SCI are still estimated to experience an average of 11 AD episodes per day [22], with episodes continuing to occur many years post-SCI [23]. The persistence of AD episodes as well as UTIs or pneumonia despite following the guidelines of best clinical practice and management, suggest the need for innovation in post-SCI care to improve long-term mortality outcomes [24].

Strengths & limitations

This study uses information from a large, nationally-representative cohort of persons admitted for first rehabilitation within a specialized SCI center in Switzerland, therefore study results are generalizable to other high-income rehabilitation settings. Unfortunately, some limitations exit. For example, many CoDs had small case numbers, thereby requiring caution when drawing conclusions from absolute numbers. Additionally, previous research has found that the CoD information coded on death certificates lacks reliability when identifying the true underlying CoD [25,26]. Assuming non-differential misclassification of codes between the GP and the TSCI population, for the present study, relative estimates of mortality would likely be attenuated towards the null, so over- or under-estimation of mortality differentials is unlikely. Another potential limitation of the current study was the use of probabilistic linkage to collect information on CoDs, and the resulting potential for incorrect linkages. However, a sensitivity analysis using secondary alternative links found no

meaningful influence on study results that would modify interpretation (Supplementary Table 4). Although unlinked deaths would bias absolute mortality rates, this study investigates relative mortality, for which unlinked deaths have been shown to have limited impact [27]. Finally, important targets for primary interventions include secondary health conditions – such as bladder control, pain, or pressure ulcers – which are notably missing from the present study. Currently, this information coupled with mortality outcomes is not available within the context of the Swiss SCI population.

Conclusion

The particularly elevated cause-specific SMRs reported within this study for cardiovascular diseases, urinary tract infections, and septicemia-related mortality require innovative approaches for management of SCI-associated secondary health conditions, as well as targeted interventions for known risk factors.

6. Statements

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7.2 Statement of Ethics

The SwiSCI cohort study has been approved by local ethics committees (reference numbers: 1008 [Luzern]; 37/11 [Basel]; CCVEM 015/11 [Valais]; 2012-0049 [Zürich]).

7.3 Disclosure Statement

The authors have no conflicts of interests to declare.

7.4 Funding Sources

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7.5 Author Contributions

JDC, MWGB and **MZ** were responsible for initial conceptual framing. **AB** and **MWGB** provided statistical support and critical feedback on manuscript content. **HPG**, **KH**, **XJ**, and **SM** provided clinical support and feedback of the present manuscript. **MZ** and **AM** provided statistical support for analyses, as well as critical evaluation of statistical methods implemented. **JDC** was responsible for all analyses, drafting, and finalization of manuscript.

7. Supplementary material

Supplementary Table 1: Causes of death and associated SMRs according to decade, not using hierarchical coding scheme

Supplementary Table 2: Competing risk analysis of risk factors for respiratory infections, subhazard ratios

Supplementary Table 3: Competing risk analysis of risk factors for UTI/renal failure, subhazard ratios

Supplementary Table 4: Causes of death and associated SMRs according to decade, alternative links

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Table 1: Causes of death stratified by total, survival one year post-injury, and SCI characteristics

		Survival more than 1 year post-injury	Completeness of SCI [Missing=17]		Level of SCI [Missing=1]	
Cause of death	**Total** (N=335)	**Total** (N=229)	**Incomplete**	**Complete**	**Tetraplegia**	**Paraplegia**
Respiratory infection (J00-J22)	19 (5.7)	13 (5.7)	13 (6.2)	6 (5.6)	4 (2.9)	15 (8.3)
Chronic obstructive pulmonary disease (J40-J47)	2 (0.6)	1 (0.4)	2 (0.9)	-	-	2 (1.1)
Other respiratory disease (J30-J99)	19 (5.7)	10 (4.4)	7 (3.3)	11 (10.3)	8 (5.8)	11 (6.1)
Cardiac disease (I05-I09; I11; I30-I59)	40 (11.9)	25 (10.9)	24 (11.4)	15 (14.0)	14 (10.1)	26 (14.4)
Ischemic heart disease (I20-I25)	34 (10.1)	28 (12.2)	28 (13.3)	5 (4.7)	11 (7.9)	21 (11.6)
Cerebral, circulatory disease (I60-I69)	13 (3.9)	11 (4.8)	10 (4.7)	2 (1.9)	3 (2.2)	9 (5.0)
Pulmonary, circulatory disease (I26-I28)	16 (4.8)	9 (3.9)	9 (4.3)	7 (6.5)	7 (5.0)	9 (5.0)
Other circulatory disease (I10; I12-I15; I70-I99)	19 (5.7)	12 (5.2)	11 (5.2)	7 (6.5)	12 (8.6)	7 (3.9)
Neoplasms (C00-D49)	27 (8.1)	21 (9.2)	20 (9.5)	4 (3.7)	13 (9.4)	13 (7.2)
Urinary infection (N390-N392)	7 (2.1)	7 (3.1)	4 (1.9)	3 (2.8)	4 (2.9)	3 (1.7)
Renal failure (N17-N19)	2 (0.6)	-	2 (0.9)	-	1 (0.7)	1 (0.6)
Digestive-related disease (K00-K95)	17 (5.1)	13 (5.7)	15 (7.1)	1 (0.9)	10 (7.2)	5 (2.8)
Suicide (X71-X83)	21 (6.3)	18 (7.9)	14 (6.6)	7 (6.5)	12 (8.6)	5 (2.8)
Accidents (S00-T88; V00-X58)	28 (8.4)	7 (3.1)	11 (5.2)	14 (13.1)	8 (5.8)	20 (11.0)
Skin-related disease (L00-L99)	1 (0.3)	1 (0.4)	-	1 (0.9)	1 (0.7)	-
Infectious disease (A00-B99, excl. A41)	4 (1.2)	3 (1.3)	2 (0.9)	2 (1.9)	3 (2.2)	-
Septicemia (A41)	7 (2.1)	5 (2.2)	4 (1.9)	3 (2.8)	3 (2.2)	4 (2.2)
Ill-defined (R00-R99)	12 (3.6)	9 (3.9)	9 (4.3)	2 (1.9)	4 (2.9)	6 (3.3)
Nervous System-related disease (G00-G99)	19 (5.7)	16 (7.0)	9 (4.3)	9 (8.4)	10 (7.2)	9 (5.0)
Endocrine-related disease (E00-E89)	9 (2.7)	7 (3.1)	3 (1.4)	5 (4.7)	4 (2.9)	4 (2.2)
Musculoskeletal-related disease (M00-M99)	7 (2.1)	4 (1.7)	7 (3.3)	-	2 (1.4)	5 (2.8)
Mental-related disease (F01-F99)	11 (3.3)	8 (3.5)	6 (2.8)	3 (2.8)	5 (3.6)	5 (2.8)
Immune, blood, eye/ear-related disease (D50-D89; H00-H59)	1 (0.3)	1 (0.4)	1 (0.5)	-	-	1 (0.6)

Table 2: All-cause standardized mortality ratios (SMRs)

	Num. of deaths	Expected deaths	SMR (95% CI)
Overall	376	162.19	2.32 (2.10-2.56)
Sex			
Male	257	116.63	2.20 (1.95-2.49)
Female	119	45.56	2.61 (2.18-3.13)
Lesion Level*			
Paraplegia	156	76.71	2.03 (1.74-2.38)
Tetraplegia	203	76.55	2.65 (2.31-3.04)
Completeness*			
Incomplete	218	116.15	1.88 (1.64-2.14)
Complete	125	32.42	3.86 (3.24-4.60)
Level & completeness*			
Incomplete paraplegia	83	50.64	1.64 (1.32-2.03)
Complete paraplegia	68	25.52	2.66 (2.10-3.38)
Incomplete tetraplegia	135	65.53	2.06 (1.74-2.44)
Complete tetraplegia	57	6.71	8.49 (6.55-11.01)

Note: *Excluding cauda equina lesions

Table 3: Cause-specific SMRs, overall and one year post-injury

				Survived at least one year post-injury	
Causes of death	**Num. of deaths**	**Expected deaths**	**SMR (95% CI)**	**Num. of deaths**	**SMR (95% CI)**
Respiratory infection	19	3.12	6.10 (3.89-9.56)	13	4.29 (2.49-7.38)
Chronic obstructive pulmonary disease	2	3.71	0.54 (0.13-2.16)	1	0.28 (0.04-1.95)
Other respiratory disease	19	5.04	3.77 (2.41-5.91)	10	2.02 (1.09-3.75)
Cardiac disease	40	10.62	3.77 (2.76-5.13)	25	2.41 (1.63-3.56)
Ischemic heart disease	34	18.27	1.86 (1.33-2.60)	28	1.56 (1.08-2.27)
Cerebral, circulatory disease	13	8.37	1.55 (0.90-2.67)	11	1.34 (0.74-2.42)
Pulmonary, circulatory disease	16	0.88	18.15 (11.12-29.63)	9	10.38 (5.40-19.95)
Other circulatory disease	19	7.21	2.50 (1.57-3.96)	12	1.70 (0.96-2.99)
Neoplasms	27	38.37	0.70 (0.48-1.03)	21	0.56 (0.36-0.85)
Urinary infection	7	0.39	18.16 (8.66-38.10)	7	18.54 (8.84-38.90)
Renal failure	2	0.65	3.06 (0.77-12.25)	0	-
Digestive disease	17	5.11	3.32 (2.07-5.35)	13	2.59 (1.50-4.45)
Suicide	21	3.16	6.65 (4.34-10.20)	18	5.76 (3.63-9.14)
Accidents	28	5.02	5.57 (3.85-8.07)	7	1.42 (0.67-2.97)
Skin-related disease	1	0.17	5.88 (0.83-41.77)	1	6.00 (0.84-42.57)
Infectious disease	4	1.54	2.59 (0.97-6.91)	3	1.97 (0.64-6.12)
Septicemia	7	0.36	19.71 (9.40-41.35)	5	14.35 (5.97-34.46)
Ill-defined	12	4.49	2.68 (1.52-4.71)	9	2.04 (1.06-3.92)
Nervous system-related disease	19	5.77	3.29 (2.10-5.16)	16	2.82 (1.73-4.61)
Endocrine-related disease	9	3.66	2.46 (1.28-4.72)	7	1.95 (0.93-4.08)
Musculoskeletal-related disease	7	1.02	6.88 (3.28-14.43)	4	4.01 (1.50-10.67)
Mental-related disease	11	6.28	1.75 (0.97-3.16)	8	1.30 (0.65-2.60)
Immune, blood, eye/ear-related disease	1	0.35	2.85 (0.40-20.27)	1	2.91 (0.41-20.65)

Table 4: Cause-specific SMRs stratified by lesion characteristics

	Para	Tetra	Incomplete	Complete
Causes of death	**SMR (95% CI)**	**SMR (95% CI)**	**SMR (95% CI)**	**SMR (95% CI)**
Respiratory infection	2.98 (1.12-7.94)	9.23 (5.57-15.32)	5.21 (3.03-8.98)	12.35 (5.55-27.50)
Chronic obstructive pulmonary disease	-	1.06 (0.27-4.24)	0.66 (0.17-2.65)	-
Other respiratory disease	3.58 (1.79-7.15)	4.33 (2.40-7.82)	1.71 (0.82-3.59)	14.12 (7.82-25.50)
Cardiac disease	2.97 (1.76-5.02)	4.85 (3.30-7.13)	2.84 (1.90-4.24)	8.73 (5.26-14.48)
Ischemic heart disease	1.35 (0.75-2.44)	2.30 (1.50-3.52)	1.91 (1.32-2.77)	1.72 (0.72-4.13)
Cerebral, circulatory disease	0.81 (0.26-2.52)	2.12 (1.10-4.07)	1.50 (0.81-2.79)	1.47 (0.37-5.87)
Pulmonary, circulatory disease	17.01 (8.11-35.68)	21.35 (11.11-41.03)	13.15 (6.84-25.26)	42.59 (20.30-89.34)
Other circulatory disease	3.44 (1.90-6.20)	1.93 (0.92-4.05)	1.73 (0.93-3.21)	6.15 (2.93-12.91)
Neoplasms	0.70 (0.41-1.21)	0.74 (0.43-1.28)	0.68 (0.44-1.05)	0.53 (0.20-1.40)
Urinary infection	23.73 (8.90-63.21)	15.17 (4.89-47.03)	12.74 (4.78-33.95)	52.54 (16.94-162.89)
Renal failure	3.42 (0.48-24.27)	3.07 (0.43-21.77)	3.76 (0.94-15.05)	-
Digestive disease	4.12 (2.22-7.65)	2.11 (0.88-5.06)	3.79 (2.28-6.28)	1.05 (0.15-7.42)
Suicide	6.82 (3.87-12.01)	4.42 (1.84-10.61)	6.63 (3.92-11.19)	7.87 (3.75-16.50)
Accidents	3.16 (1.58-6.31)	9.37 (6.04-14.52)	3.01 (1.67-5.43)	12.48 (7.39-21.07)
Skin-related disease	12.93 (1.82-91.76)	-	-	34.50 (4.86-244.88)
Infectious disease	3.90 (1.26-12.09)	-	1.76 (0.44-7.03)	5.89 (1.47-23.54)
Septicemia	18.54 (5.98-57.47)	23.04 (8.65-61.38)	14.20 (5.33-37.83)	50.09 (16.16-155.31)
Ill-defined	1.86 (0.70-4.96)	2.92 (1.31-6.50)	2.61 (1.36-5.02)	2.31 (0.58-9.24)
Nervous system-related disease	3.79 (2.04-7.04)	3.20 (1.66-6.15)	1.97 (1.03-3.79)	9.07 (4.72-17.42)
Endocrine-related disease	2.36 (0.89-6.29)	2.27 (0.85-6.04)	1.05 (0.34-3.25)	7.65 (3.18-18.37)
Musculoskeletal-related disease	4.30 (1.08-17.20)	10.04 (4.18-24.11)	8.78 (4.19-18.41)	-
Mental-related disease	1.74 (0.73-4.19)	1.64 (0.68-3.94)	1.21 (0.54-2.69)	2.81 (0.91-8.72)
Immune, blood, eye/ear-related disease	-	5.96 (0.84-42.28)	3.68 (0.52-26.09)	-

Note: SMRs not calculated for those CoDs with insufficient cases.

Table 5: Competing risk analysis of risk factors for cause-specific mortality, subhazard ratios

	Respiratory diseases (N=21)		Cardiovascular diseases (N=122)		Neoplasms (N=27)	
	Univariable	Multivariable	Univariable	Multivariable	Univariable	Multivariable
Age at injury						
Less than 46 years	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
46-60 years	6.59 (0.74-58.96)	5.07 (0.53-48.83)	2.63 (1.09-6.33)	2.48 (1.02-5.99)	5.67 (1.18-27.29)	3.56 (0.69-18.38)
60 years and older	28.94 (3.84-218.26)	27.71 (3.62-212.31)	22.34 (10.86-45.94)	16.43 (7.87-34.31)	15.71 (3.63-68.01)	9.91 (2.24-43.78)
Lesion Level						
Paraplegia	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Tetraplegia	2.60 (1.08-6.28)	3.37 (1.29-8.80)	2.58 (1.79-3.73)	2.22 (1.50-3.30)	1.68 (0.78-3.63)	1.45 (0.62-3.37)
Completeness						
Incomplete	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Complete	2.25 (0.93-5.42)	4.95 (1.97-12.46)	0.78 (0.52-1.15)	1.50 (0.99-2.28)	0.36 (0.12-1.06)	0.55 (0.18-1.66)
	Infections (N=37)		Accidents (N=28)		Other (N=100)	
	Univariable	Multivariable	Univariable	Multivariable	Univariable	Multivariable
Age at injury						
Less than 46 years	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
46-60 years	0.69 (0.18-2.68)	0.67 (0.17-2.59)	1.43 (0.48-4.25)	1.38 (0.42-4.53)	1.44 (0.73-2.82)	1.16 (0.58-2.34)
60 years and older	6.87 (2.98-15.82)	5.53 (2.34-13.07)	3.74 (1.52-9.18)	3.57 (1.33-9.60)	5.75 (3.38-9.78)	4.31 (2.48-7.49)
Lesion Level						
Paraplegia	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Tetraplegia	2.65 (1.35-5.17)	2.65 (1.32-5.34)	3.79 (1.67-8.60)	3.93 (1.65-9.37)	1.41 (0.93-2.14)	1.30 (0.83-2.02)
Completeness						
Incomplete	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Complete	1.09 (0.56-2.13)	1.96 (0.96-4.00)	2.40 (1.09-5.30)	4.25 (1.86-9.72)	0.82 (0.52-1.29)	1.15 (0.72-1.84)

Note: The group "Respiratory diseases" excludes respiratory infections, while the group "Infections" includes respiratory infections, septicemia, urinary tract infections, and all other infections. Sex and cause of TSCI were included in the analyses as potential confounders.

Supplementary Table 1: Causes of death and associated SMRs according to decade, not using hierarchical coding scheme

Causes of death	Actual number of deaths	Expected deaths	SMR (95% Confidence Interval)	Comparison with SMRs using heirarchy
Respiratory infection	6	3.12	1.93 (0.87-4.29)	↓†
Chronic obstructive pulmonary disease	1	3.71	0.27 (0.04-1.91)	‡↓
Other respiratory	7	5.04	1.39 (0.66-2.91)	†↓
Cardiac disease	23	10.62	**2.17 (1.44-3.26)**	‡↓
Ischemic heart disease	30	18.27	**1.64 (1.15-2.35)**	‡↓
Cerebral, circulatory	13	8.37	1.55 (0.90-2.67)	‡
Pulmonary, circulatory	6	0.88	**6.81 (3.06-15.15)**	‡↓
Other circulatory	12	7.21	1.66 (0.94-2.93)	†↓
Neoplasms	27	38.37	0.70 (0.48-1.03)	‡
Urinary infection	3	0.39	**7.78 (2.51-24.13)**	‡↓
Digestive	17	5.11	**3.32 (2.07-5.35)**	‡
Suicide	21	3.16	**6.65 (4.34-10.20)**	‡
Accidents	88	5.02	**17.52 (14.22-21.59)**	‡↑
Skin	1	0.17	5.88 (0.83-41.77)	‡
Infectious	4	1.54	2.59 (0.97-6.91)	‡
Septicemia	3	0.36	8.45 (2.72-26.20)	‡↓
Ill-defined	11	4.49	2.45 (1.36-4.43)	‡
Nervous	44	5.77	7.62 (5.67-10.24)	‡↑
Endocrine	5	3.66	1.36 (0.57-3.28)	N.A.
Musculoskeletal	5	1.02	4.91 (2.05-11.81)	‡↓
Mental	6	6.28	0.96 (0.43-2.13)	↓†

Legend

Increased	↑
Remained significant/non-significant	‡
Decreased	↓
No longer significant	†

Supplementary Table 2: Competing risk analysis of risk factors for respiratory infections, subhazard ratios

	Respiratory Infection		**All other causes**	
	Hierarchical coding (N=19)	SA coding scheme (N=44)	Hierarchical coding (N=316)	SA coding scheme (N=291)
Age at injury				
Less than 46 years	Ref.	Ref.	Ref.	Ref.
46-59 years	3.16 (0.21-47.55)	1.54 (0.49-4.83)	1.53 (1.23-1.90)	1.57 (1.28-1.92)
60 years and older	21.65 (1.31-356.75)	16.89 (6.22-45.88)	7.17 (6.16-8.34)	6.78 (5.79-7.94)
Lesion Level				
Paraplegia	Ref.	Ref.	Ref.	Ref.
Tetraplegia	5.90 (2.35-14.76)	3.02 (1.12-8.17)	1.90 (1.46-2.47)	1.90 (1.42-2.52)
Completeness				
Incomplete	Ref.	Ref.	Ref.	Ref.
Complete	2.01 (1.34-3.04)	1.62 (1.06-2.47)	1.58 (1.26-1.98)	1.60 (1.28-2.00)

* Notes: (1) "SA coding schema" refers to the identification of a "respiratory infection" ICD code anywhere on death certificate (i.e., underlying CoD, initial disease, consecutive, or concomitant). For example, individuals coded under the hierarchical coding schema as having died from a cardiovascular-related disease, but for which the respiratory infection code was included as a concomitant disease, would be included as having died due to a respiratory infection in the SA coding schema. (2) Cause of SCI and sex were also included within the multivariable models as potential confounders.

Supplementary Table 3: Competing risk analysis of risk factors for UTI/renal failure, subhazard ratios

	Respiratory Infection		All other causes	
	Hierarchical coding (N=19)	SA coding scheme (N=44)	Hierarchical coding (N=316)	SA coding scheme (N=291)
Age at injury				
Less than 46 years	Ref.	Ref.	Ref.	Ref.
46-59 years	1.51 (1.30-1.75)	2.25 (2.06-2.47)	1.57 (1.23-2.00)	1.53 (1.21-1.94)
60 years and older	10.46 (3.04-35.99)	14.87 (4.98-44.39)	7.44 (6.54-8.47)	7.15 (6.18-8.27)
Lesion Level				
Paraplegia	Ref.	Ref.	Ref.	Ref.
Tetraplegia	1.16 (0.39-3.44)	1.11 (0.48-2.56)	2.05 (1.57-2.69)	2.13 (1.59-2.86)
Completeness				
Incomplete	Ref.	Ref.	Ref.	Ref.
Complete	1.33 (0.55-3.21)	1.27 (0.66-2.45)	1.61 (1.27-2.04)	1.63 (1.24-2.15)

* Notes: (1) "SA coding schema" refers to the identification of a UTI or renal failure ICD code anywhere on death certificate (i.e., underlying CoD, initial disease, consecutive, or concomitant). For example, individuals coded under the hierarchical coding schema as having died from a cardiovascular-related disease, but for which the renal failure code was included as a concomitant disease, would be included as having died due to UTI/renal failure in the SA coding schema. (2) Cause of SCI and sex were also included within the multivariable models as potential confounders.

Supplementary Table 4: Causes of death and associated SMRs according to decade, alternative links

			Alternative link	Primary link
Causes of death	**Actual number of deaths**	**Expected deaths**	**SMR (95% Confidence Interval)**	**SMR (95% Confidence Interval)**
Respiratory infection	17	3.12	5.46 (3.39-8.78)	6.10 (3.89-9.56)
Chronic obstructive pulmonary disease	3	3.71	0.81 (0.26-2.51)	0.54 (0.13-2.16)
Other respiratory	19	5.04	3.77 (2.41-5.91)	3.77 (2.41-5.91)
Cardiac disease	38	10.62	3.58 (2.60-4.92)	3.77 (2.76-5.13)
Ischemic heart disease	34	18.27	1.86 (1.33-2.60)	1.86 (1.33-2.60)
Cerebral, circulatory	12	8.37	1.43 (0.81-2.52)	1.55 (0.90-2.67)
Pulmonary, circulatory	15	0.88	17.01 (10.26-28.22)	18.15 (11.12-29.63)
Other circulatory	17	7.21	2.36 (1.47-3.79)	2.50 (1.57-3.96)
Neoplasms	25	38.37	0.65 (0.44-0.96)	0.70 (0.48-1.03)
Urinary infection	7	0.39	18.16 (8.66-38.10)	18.16 (8.66-38.10)
Renal failure	2	0.65	3.06 (0.77-12.25)	3.06 (0.77-12.25)
Digestive	17	5.11	3.32 (2.07-5.35)	3.32 (2.07-5.35)
Suicide	20	3.16	6.34 (4.09-9.82)	6.65 (4.34-10.20)
Accidents	25	5.02	4.98 (3.36-7.37)	5.57 (3.85-8.07)
Skin	1	0.17	5.88 (0.83-41.77)	5.88 (0.83-41.77)
Infectious	4	1.54	2.59 (0.97-6.91)	2.59 (0.97-6.91)
Septicemia	7	0.36	19.71 (9.40-41.35)	19.71 (9.40-41.35)
Ill-defined	12	4.49	2.68 (1.52-4.71)	2.68 (1.52-4.71)
Nervous	18	5.77	3.12 (1.96-4.95)	3.29 (2.10-5.16)
Endocrine	8	3.66	2.18 (1.09-4.37)	2.46 (1.28-4.72)
Musculoskeletal	7	1.02	6.88 (3.28-14.43)	6.88 (3.28-14.43)
Mental	12	6.28	1.91 (1.09-3.37)	1.75 (0.97-3.16)
Immune, blood, eye/ear	1	0.35	2.85 (0.40-20.27)	2.85 (0.40-20.27)